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10/705,389	11/10/2003	Narayanan Sundararajan	21058/1206459-US2	4354

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EXAMINER

SISSON, BRADLEY L

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

05/28/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/705,389

Applicant(s)

SUNDARARAJAN ET AL.

Examiner

Bradley L. Sisson

Art Unit

1634

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2008.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 46-94 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 46-94 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 10 November 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date 11/28/2007 & 3/31/2008
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Drawings

1. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

- a. The lettering is not of proper size, uniform density, and well-defined in Figure(s) 11; and
- b. The lines are not clean, well-defined, and of uniform thickness in Figure(s) 11;

2. Attention is directed to the following section of 37 CFR 1.84.

(l) *Character of lines, numbers, and letters.* All drawings must be made by a process which will give them satisfactory reproduction characteristics. Every line, number, and letter must be durable, clean, black (except for color drawings), sufficiently dense and dark, and uniformly thick and well-defined. The weight of all lines and letters must be heavy enough to permit adequate reproduction. This requirement applies to all lines however fine, to shading, and to lines representing cut surfaces in sectional views. Lines and strokes of different thicknesses may be used in the same drawing where different thicknesses have a different meaning.

(m) *Shading.* The use of shading in views is encouraged if it aids in understanding the invention and if it does not reduce legibility. Shading is used to indicate the surface or shape of spherical, cylindrical, and conical elements of an object. Flat parts may also be lightly shaded. Such shading is preferred in the case of parts shown in perspective, but not for cross sections. See paragraph (h)(3) of this section. Spaced lines for shading are preferred. These lines must be thin, as few in number as practicable, and they must contrast with the rest of the drawings. As a substitute for shading, heavy lines on the shade side of objects can be used except where they superimpose on each other or obscure reference characters. Light should come from the upper left corner at an angle of 45°. Surface delineations should preferably be shown by proper shading. Solid black shading areas are not permitted, except when used to represent bar graphs or color.

(n) *Symbols.* Graphical drawing symbols may be used for conventional elements when appropriate. The elements for which such symbols and labeled representations are used must be adequately identified in the specification. Known devices should be illustrated by symbols which have a universally recognized conventional meaning and are generally accepted in the art. Other symbols which are not universally recognized may be used,

subject to approval by the Office, if they are not likely to be confused with existing conventional symbols, and if they are readily identifiable.

(o) *Legends.* Suitable descriptive legends may be used subject to approval by the Office, or may be required by the examiner where necessary for understanding of the drawing. They should contain as few words as possible.

(p) *Numbers, letters, and reference characters.*

(1) Reference characters (numerals are preferred), sheet numbers, and view numbers must be plain and legible, and must not be used in association with brackets or inverted commas, or enclosed within outlines, e.g., encircled. They must be oriented in the same direction as the view so as to avoid having to rotate the sheet. Reference characters should be arranged to follow the profile of the object depicted.

(2) The English alphabet must be used for letters, except where another alphabet is customarily used, such as the Greek alphabet to indicate angles, wavelengths, and mathematical formulas.

(3) Numbers, letters, and reference characters must measure at least .32 cm. (1/8 inch) in height. They should not be placed in the drawing so as to interfere with its comprehension. Therefore, they should not cross or mingle with the lines. They should not be placed upon hatched or shaded surfaces. When necessary, such as indicating a surface or cross section, a reference character may be underlined and a blank space may be left in the hatching or shading where the character occurs so that it appears distinct.

3. Applicant is advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended

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drawing(s) must not be labeled as “amended.” If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor’s name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as “Annotated Sheet” and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the “Notice of Allowability.” Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Specification

4. On 28 July 2006 applicant amended the specification to correct for a trademark. A review of the specification finds numerous other trademarks that have not been addressed. Those other trademarks are: APPLIED BIOSYSTEMS, TRITON, MOLECULAR PROBES, NANOGOLD, NANOPROBES, PENTIUM, CELERON, INTEL, ITANIUM, XEON, PRISM, SEQUENCHER, and GENE CODES. They should be capitalized wherever they appear and be accompanied by their respective generic terminology.

5. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

6. Claims 46, 49, 56, 59, 66, 69, 76, and 79 are objected to because of the following informalities: Said claims refer to a "mass dependent property." Said expression should be written as >>mass-dependent property<<. Similarly, claim 49, 50, 59, 60, 69, 70, and 79 are objected to as the expression "resonant frequency shifts" should appear as >>resonant-frequency shifts<<. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 46-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 46 with the added limitations that the template is single stranded DNA, and that a primer has annealed to the template, that a single nucleotide is added to the reaction mixture, that unincorporated nucleotides are removed prior to the unblocking of any incorporated nucleotide, that the primer has annealed to but a single site on the template, that the template does not form duplex structures with self and therein provide a second point for nucleotide incorporation, and that the nucleic acid being sequenced has some

utility, does not reasonably provide enablement for the sequencing of any and all manner of nucleic acids, or for the sequencing of nucleic acids where multiple nucleotides are present in the reaction mixture and it is not possible to differentiate between them. Also, the specification does not enable the method to the extent that it encompasses . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. As presently worded, the "template nucleic acid molecule" is to range "from about 10 to approximately 100,000 nucleotides in length" and is also required to be "partially double stranded." Such requirements fairly encompass intact plasmids that have a mismatch somewhere within. Similarly, the claimed method fairly encompasses tRNA as the template. It is noted that tRNA comprises numerous double stranded regions, all of which are the result of self hybridization, and none of which offer a terminus for sequencing. And the claimed method fairly encompasses a length of chromosomal DNA that has a plurality of primers annealed thereto. The primers need not be the same. In such a situation, the probability of a single nucleotide being incorporated at any one location increases significantly. The specification is silent as to how one would be able to determine the correct nucleotide sequence of a template nucleic acid when multiple primers are annealed at different locations of the template. While one may well be able to determine the nucleotide being incorporated, e.g., a single nucleotide being used at a time, the ordinary artisan would not be able to determine just where it was incorporated.

9. As presently worded, one is to determine/identify the nucleotide that was incorporated into the "template," and based on such identification, one is to then determine the sequence of the "template." For purposes of examination, the "template" has been construed as the strand to

which the complementary nucleotide anneals, not the strand to which the nucleotide is incorporated. The specification has not been found to set forth a reproducible process whereby one would be able to determine the nucleotide sequence of a nucleic acid of any length by simply adding a nucleotide to its 3'-terminus. Applicant is urged to consider further clarifying the aspect of the double-stranded region, and the strand to which the nucleotide is being incorporated.

10. As presently worded, the claimed method fairly encompass the removal of al incorporated nucleotides that have any mass-dependent property, and then insert a nucleotide that lacks a mass-dependent property (see, e.g., claims 90-93). A review of the specification fails to find where the essential starting materials and reaction conditions have been set forth such that one would be able to determine when, if at all, all of the excised nucleotides have been removed and/or unlabeled nucleotides have been inserted for all positions, and not for any position that has not been previously interrogated/identified with a mass-dependent label.

11. In accordance with claims 53, 54, 63, 64, 73, 74, 83, and 84, one is to hybridize a primer to the template and to use a polymerase to attach a nucleotide to the 3' end of the primer. In recognizing that each of said claims depends from an independent claim, and that each of said independent claims requires the addition of a modified nucleotide to the partially double-stranded template nucleic acid, the aspect of hybridizing a primer would result in there being a plurality of sites at which a nucleotide is being added. Further, with said claims requiring the use of a polymerase, all remaining claims fairly encompass practicing the claimed method where no polymerase is being used. A review of the disclosure fails to find where applicant had enabled the method by use of anything other than a polymerase.

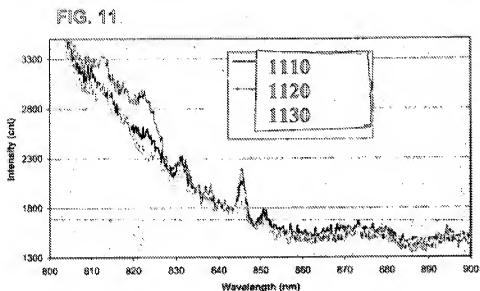
12. In accordance with new claims 86-89, the “mass labels are selected from the group consisting of nanoparticles, nanoparticle aggregates, carbon nanotubes, fullerenes, functionalized fullerenes, functionalized fullerenes, quantum dots, dendrimers, and combinations thereof.” A review of the disclosure fails to find where applicant has set forth the essential starting materials and reaction conditions whereby any combination of such labels can be used in a reproducible manner, resulting in the accurate and reproducible sequencing of any nucleic acid.”

13. A review of the disclosure finds the following examples:

- a. Example 1, p. 23, “Standard *in situ* hybridization conditions;”
- b. Example 2, pp. 23-24, “Standard *in situ* hybridization conditions;”
- c. Example 3, pp. 24-26, “Exemplary method for preparing DNA to make RNA templates;”
- d. Example 5, pp. 36-37; refers to Fig. 11, which is asserted as illustrating Raman spectra of dATP solution before and after incorporation.

14. It is noted that a review of the disclosure fails to locate an “Example 4.”

15. A review of the disclosure fails to find where any nucleic acid of any length, much less a nucleic acid of 100,000 nucleotides has been accurately sequenced by any method. While Example 5 refers to Figure 11, it is noted that Figure 11 does not depict the reading of a shift in a resonance of a cantilever upon incorporation of a nucleotide in an attached template nucleic acid that ranges from about 10 to about 100,000 nucleotides in length. Rather, Fig. 11, refers to UV absorbance of dATP upon incorporation by a primer wherein the primer is bound to a plastic support; see below.



16. In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled for the full scope of protection sought.

Conclusion

17. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634